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Beyond Sodium, Phosphate and Potassium: Potential Dietary Interventions in kidney Disease

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Abstract

People with kidney disease are advised to restrict individual nutrients, such as sodium, potassium and phosphate, in line with current best practice guidelines. However, there is limited evidence to support the efficacy of single nutrient strategies, and compliance remains a challenge for clinicians to overcome. Many factors are known to contribute to poor compliance with dietary prescriptions, including conflicting priorities for single nutrient restriction, the arduous self-monitoring required, and the health-related knock-on effects resulting from targeting these nutrients in isolation. This paper reviews the evidence-base for the overall pattern of eating as a potential tool to deliver a diet intervention in which all the nutrients and foods work cumulatively and synergistically to improve clinical outcomes. These interventions may assist in kidney disease management and overcome these innate challenges that single nutrient interventions possess. The characteristics of healthy dietary patterns are that they are typically plant-based and lower in sodium and animal proteins. These patterns may have numerous mechanistic benefits for cardiovascular health in kidney disease, most notably through the increase in fruit, vegetables, and a higher protein ratio from plant-based sources, and improved gut health through the increase in dietary fiber. The evidence to date for dietary patterns points towards a predominant plant-based diet, and suggests these diet interventions may better translate to improved clinical outcomes in kidney disease. However, for this type of dietary pattern to be translated into practice, clinical trials are needed to determine whether these diet interventions are feasible, safe and effective in the management of kidney disease.

Background

Diet has long been considered a modifiable risk factor for chronic kidney disease (CKD), and a key management strategy in end-stage kidney disease (ESKD). International guidelines for managing kidney disease have traditionally focused on the modification of the macro- and micro-nutrients such as protein, energy, sodium, potassium, phosphorous, and types of macronutrients, including fatty acids and sugars.^{1, 2} This approach of individual nutrient modification can result in complex nutrition messages. Translating these into clear food-based recommendations is challenging. It comes as little surprise that food and fluid advice have been reported as ambiguous and frustrating by patients,³ inherently restrictive⁴ and have been shown to adversely impact overall diet quality.⁵

The aim of dietary management in patients with early stage CKD is to delay progression and reduce cardiovascular risk. Conversely, in dialysis patients, the focus is to mitigate protein-energy wasting and electrolyte disturbances (i.e. low potassium, low phosphorous, high calorie).⁶ In contrast, a traditional cardio-protective diet targeting higher fiber, and lower saturated fat may be considered to be in direct conflict with low electrolyte and high calorie advice in CKD management.⁷ Adopting an alternative whole-of-diet approach, which shifts focus onto foods, such as wholegrains, fruits, and vegetables, shows considerable promise with respect to pragmatically and effectively achieving the universal goals of retarding CKD progression and attenuating cardiovascular risk, whilst still avoiding serious electrolyte derangements.^{4, 8}

This paper will consider historical evidence for individual nutrient-based restrictions, appraise and contrast new evidence and controversies, and discuss emerging, whole-of-diet strategies for the management of kidney disease and its complications.

Challenges with traditional individual nutrient approaches to nutrition management

Current international guidelines recommend patients receive individualised dietary interventions by a qualified dietitian focusing on individual nutrients, including salt, phosphate, potassium, protein and calories.^{2, 9-12} These traditional single-nutrient focus recommendations present four key issues:

a) Poor evidence base underpinning individual nutrient strategies

Most studies examining individual nutrient modification strategies have been limited in methodologic quality. Studies in nutritional nephrology are plagued by small sample sizes, short follow-up and use of non-validated surrogate outcome measures,^{2, 13-17} such that the effects of these approaches on patient-level outcomes, including ESKD and mortality, remain uncertain. For example, dietary salt reduction is considered a key dietary strategy in kidney disease, with strong evidence supporting a role for augmenting the pharmacological effects of antihypertensive medications and reducing blood pressure and albuminuria. However, the effects of long-term salt restriction on CKD progression and cardiovascular outcomes remain uncertain.¹⁷⁻²² Similarly, dietary phosphate restriction has been advocated by many guidelines to ameliorate renal and cardiovascular risk. However, the evidence that change to dietary phosphorus intake can impact outcomes beyond serum measures is notably absent.^{23, 24} Dietary potassium restriction for the prevention and management of hyperkalaemia is further advocated, particularly in more advanced forms of CKD, and ensuing cardiac arrhythmias. However, to date there have been no randomised-controlled trials evaluating the impact of potassium restriction on clinical events. In contrast, increased dietary potassium consumption is advocated in concert with dietary sodium restriction to reduce cardiovascular risk in the general population.²⁵ There is observational evidence of the benefits of this in CKD models on CV risk factors,²⁶ which provides further uncertainty.

Modified protein diets continue to be at the forefront of nutritional management for people with kidney disease. Low protein diets are favoured in CKD for ameliorating uraemia, kidney stone formation, gout, hyperphosphatemia, and gut-derived uremic toxins.²⁷ However, protein restriction trials report inconsistent findings and at best, provide a modest benefit for progression to ESKD²⁸ or mortality.²⁹ Meta-analysis shows protein reductions of 0.2g/kg/day delay CKD progression by only 0.5mL/min/year in both randomised and non-randomised trials.³⁰ In addition, compliance with low protein diets is poor,^{5, 31} and can risk protein-energy wasting.^{30, 32} It should therefore come as no surprise that there is a paucity of evidence supporting the assertion that low protein diets reduce the risk of progression to ESKD²⁸ or mortality.²⁹ As in CKD, the majority of evidence in dialysis is based on observational studies, and in many instances the target protein intakes are rarely achieved.³³ This continues to challenge guidelines committees tasked with designing evidence-based protein recommendations.

b) Complex nutritional interventions impair dietary adherence

Individual nutrient modification can lead to complex nutritional messages, which people with kidney disease report to be confusing and constraining.^{3-5, 34} Patients with CKD report dietary interventions to be burdensome³⁵ leading to overall poor adherence to dietary restrictions.^{5, 36} A number of characteristics are known to influence a patient's ability to follow dietary recommendations, including a patient's knowledge, self-efficacy, motivation, and uremic-related factors.³⁷ Poor dietary adherence in CKD and dialysis populations may therefore place patients at risk of clinical complications, such as malnutrition, fluid overload and CVD.^{5, 36, 38}

c) Conflict between competing priorities of individual nutrient strategies

When adopting an individual nutrient approach, translating these recommendations to food-based advice can create conflicting priorities. A key example is between dietary protein and

phosphorous. In dialysis, a high protein intake with optimal phosphate management is associated with the best survival.³⁹ However, advice to increase protein intake to prevent protein-energy wasting may in fact introduce an increase in phosphorous intake due to the high phosphorous content in protein sources. As a result, this approach can compete with an increased risk of hyperphosphatemia.³⁹

d) Health-related knock-on effects from restricting single nutrients

As mentioned above, despite the evidence-base supporting the restriction of single nutrients, this is a challenging and complex task for people with kidney disease. In addition, the practical application of these individual nutrient restrictions can compromise the overall quality of the diet and be detrimental to one's health. For example, a dialysis patient may be instructed to restrict their potassium intake by fruits, vegetables and whole grains. The 'knock-on' consequences impact both nutrition and overall health. For example, avoiding these foods reduces the exposure to dietary fiber, limiting its therapeutic role in preventing constipation and as a pre-biotic in maintaining a healthy gut microbiome.⁴⁰

Therefore, quantifying nutrient intake is not only a challenge for clinicians given poor quality evidence and risk adverse health outcomes,^{2, 9-11} but presents an intense burden for people with kidney disease to implement day-to-day, and presents conflicting priorities which risk knock-on health consequences.

A move to dietary patterns: A potential paradigm shift in kidney disease

The change in dietary management of chronic diseases from a single nutrient focus, towards the overall patterns of eating may address some of these concerns. Dietary patterns consider the cumulative effect and synergy between the combinations of foods and nutrients, which are more applicable to chronic disease management.^{41, 42} Healthy dietary patterns with evidence for mitigating CVD risk include the Dietary Approaches to Stop Hypertension (DASH) diet,⁴³

the Mediterranean diet,⁴⁴ vegetarian diets,^{45, 46} and patterns of eating consistent with dietary guidelines.^{47, 48} Observational studies suggest these mentioned dietary patterns may be superior to single nutrient interventions,⁴⁹ particularly due to the cumulative effects of multiple nutrients consumed through diets rich in fruit and vegetables,⁵⁰ fish and omega-3 fatty acids,⁵¹ legumes, wholegrain cereals and nuts,⁵² and lower in sodium,¹⁹ red meat,⁵³ saturated fats,⁵⁴ and common phosphate additives.⁵⁵

There is a paucity of evidence for the effectiveness of changing dietary patterns in the established CKD population. However, emerging data supports dietary patterns that follow the Healthy Eating Index, DASH, and the Mediterranean diet to be associated with reduced renal-related mortality and progression to ESKD.^{49, 56, 57} Preliminary data also suggest that adherence to the DASH diet may reduce the risk of ESKD incidence in people with established CKD,⁵⁸ and a small single arm trial demonstrated the DASH diet as safe in a CKD sample.⁵⁹ Other studies demonstrate that the DASH dietary pattern is associated with preserved residual kidney function and reduced overall incidence of CKD in community-dwelling individuals.^{56, 60, 61}

Similarly, the Mediterranean diet has long-standing associations with reduced CVD incidence and mortality in the non-CKD population.⁶²⁻⁶⁵ Within the CKD population specifically, it appears that the Mediterranean diet may be particularly effective in reducing systemic inflammation and microalbuminuria.⁶⁶ While no randomised controlled trials have been conducted in established CKD or dialysis populations to examine the effects of these diets on long-term patient-level outcomes, a recent meta-analysis of longitudinal studies demonstrated a healthy eating pattern was consistently associated with a 27% reduced risk of mortality in populations with established kidney disease.⁸

How can whole-of-diet approaches improve health outcomes?

The opportunity to educate people with kidney disease to achieve a healthy dietary pattern presents itself with many benefits in comparison to isolated nutrient interventions. The translation of nutrient-based recommendations is exceptionally challenging for patients to quantify without ongoing guidance and feedback on daily consumption of these nutrients.³⁴ In contrast, behavioural counselling to achieve a desired pattern of eating can lead to better compliance due to offering flexibility, choices to suit individual preferences, and a manageable change to a multitude of nutrients within the whole diet concurrently.³⁴

Adopting a healthy dietary pattern has many mechanisms of benefit for cardiovascular health in CKD, most notably through the increase in fruit, vegetables and a predominance of plant-based protein.

Fruit and vegetables and cardiovascular health in kidney disease

Fruit and vegetables generate bicarbonate naturally as they release potassium-salts and decrease the renal acid load. In-fact, a diet higher in fruit and vegetable has been shown to more effectively manage metabolic acidosis compared to standard bicarbonate prescriptions.⁶⁷ In contrast, sulphur containing animal proteins are naturally acid-producing and can exacerbate acidosis.⁵⁸ Plant-based diets also limit the bioavailability of dietary phosphorus thereby decreasing absorption (due to the presence of phytate in vegetable forms of phosphorous),⁶⁸ particularly in comparison to higher animal protein diets.⁴⁵ Plant-based diets are also characteristically higher in fruit, vegetables and wholegrains, which increase the exposure to dietary fiber, which in turn is linked to reduced inflammation and improved survival.⁶⁹

Plant-based dietary patterns have different animal-plant protein ratios

Altering the red meat-to-plant-based protein ratio to favour higher plant-based proteins has been described as likely ‘kidney sparing’ in CKD.^{53, 70} Balanced portions from both red meat, fish and plant-based sources have been demonstrated in a cohort of 1355 haemodialysis patients

to be associated with an appreciably lower risk of cardiovascular hospitalization death due to any cause compared with an unbalanced diet.⁷¹ However, despite the theoretical benefits of a plant-based diet, studies regarding the safety and efficacy of increased fruit and vegetable intake over the long term are lacking in both CKD and dialysis populations. This evidence gap needs addressing before such diets can become routinely recommended in the kidney disease population.

Safety profile of a plant-based dietary pattern in the kidney disease population

Safety concerns regarding plant-based diets relate to the high fruit and vegetable intake. However, fruit and vegetable intake is typically low across the CKD spectrum and unnecessary restriction may risk many vitamin and mineral insufficiencies.⁵ While fruit and vegetable intake conveys higher dietary potassium, it has been recently argued this does not necessarily translate into hyperkalaemia.⁷² It was also recently demonstrated that adults with stage 4 CKD can safely increase their servings of fruit and vegetables to correct metabolic acidosis and reduce blood pressure without an appreciably increased incidence of hyperkalaemia.^{73, 74} In addition, a higher fiber intake from a higher fruit and vegetable diet can prevent constipation in dialysis populations and facilitate faecal excretion of excess potassium, which can be up to 3.5 times greater than that of the general population, and is directly associated with dietary intake.⁷⁴ This ability of intestinal potassium excretion to compensate for a reduction in renal potassium handling has called into question the priority for dietary restriction in hyperkalemic states.⁷² Nonetheless, efficacy trials are needed to confirm the safety of plant-based diets.

Dietary patterns and manipulation of the gut microbiome

The bacterial community in the gut (termed the microbiota) contributes to digestion through fermentation and putrefaction,⁷⁵ and is able to be manipulated by plant-based dietary patterns which emphasize whole grain carbohydrates, higher intakes of fibrous fruits, vegetables,

legumes and nuts.^{75, 76} Gut dysbiosis is commonly observed in kidney disease populations and is a major contributor to the build-up of uraemic toxins. Indoxyl sulphate (IS) and p-cresyl sulphate (PCS) are two uremic toxins produced by the gut microbiome, which originate from protein metabolism in the gut and are associated with increased CVD risk.⁷⁷

It has been established that the concentration of these uremic toxins is increased by a high protein-to-fiber ratio in the diet.⁷⁸ Higher protein diets promote proteolytic (putrefaction) bacteria over saccharolytic (fermentation) bacteria, which in turn contributes to dysbiosis and a higher risk of CVD.⁷⁹ Protein metabolism in the gut leads to the breakdown of tyrosine, phenylalanine, and tryptophan which are known precursor products for PCS and IS conversion.⁷⁹ In contrast, the fermentation of fiber (non-digestible carbohydrate) releases short-chain fatty acids that are known to favour healthy microbial activity to control dysbiosis.⁸⁰ Populations consuming a predominantly plant-based diet have greater microbiome abundance and biodiversity compared with populations consuming a diet subject to processing and inadequate fiber.⁸¹ A high fiber vegetarian diet has also been shown to reduce the production of IS and PCS compared to a high meat diet in a healthy population,⁴⁶ which might translate to a reduced risk of CVD and mortality.

In the kidney disease population specifically, recent trials have demonstrated the roles of pre-biotics,⁸² pro-biotics,⁸³ and their combination as synbiotics⁸⁴ to modulate the composition of the intestinal microbiota, thereby controlling the production of IS and PCS, and ultimately potentially mitigating CVD risk and mortality.⁸⁵ Improving the microbial diversity through synbiotics in kidney disease populations highlights an important role of the gut in mediating CVD risk, but also reaffirms the role of the overall quality of the diet. Specifically, a plant-based dietary pattern which contain natural pre-biotics⁸⁶ and is lower in red meat proteins represents an important strategy for reducing uremic toxin production naturally.⁴⁶ This dietary pattern is more likely to support the production of saccharolytic

bacteria, generate short-chain fatty acids and improve cardiovascular risk and gastrointestinal health overall, beyond that of the single nutrient strategies targeting prebiotics, fiber, carbohydrates or protein in isolation.^{78, 87}

Is a new paradigm shift in renal nutrition management on the horizon?

People with kidney disease are advised to restrict individual nutrients, in line with current best practice guidelines. However, patients face several challenges from conflicting priorities which often result in poor compliance. Recent evidence supports a shift in nutritional focus to a healthy dietary pattern which is predominantly plant-based to promote control over a range of clinical risk factors and end-points in kidney disease. This is likely an approach which could facilitate compliance with dietary change in kidney disease. In addition, the non-invasive manipulation of the gut microbiota through a plant-based diet which is high in natural prebiotics has promising clinical potential.

It is now timely to determine whether a predominantly plant-based diet is feasible, safe and effective in the management of CKD and dialysis. To test the important question of whether the adoption of healthy eating patterns could improve patient-level outcomes in the kidney disease population, high quality controlled clinical trials are needed. However, until a plant-based dietary pattern has been deemed both safe and effective, and tested using a pragmatic implementation strategy, these theories of what exactly constitutes a ‘healthy’ diet will continue to be hypothetical.

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